Functional Maturation of hPSC-Derived Forebrain Interneurons Requires an Extended Timeline and Mimics Human Neural Development.

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Public Summary:
The creation of mature human nerve cells from stem cells has seen significant progress in recent years. There is great interest in the generation of cortical inhibitory interneurons, cells that could have important applications in the treatment of epilepsy and other neurological diseases. In this paper we report in vitro conditions that allow for the derivation of human interneurons, from stem cells. These newly made interneurons behave similarly in vitro and in vivo to some classes of interneurons found in the human body. We also report the successful transplantation and integration of these interneurons into the brains of rodents. These stem cell derived interneurons provide a source of cells that can be either transplanted for disease treatment or studied to model disease behaviour.

Scientific Abstract:
Directed differentiation from human pluripotent stem cells (hPSCs) has seen significant progress in recent years. However, most differentiated populations exhibit immature properties of an early embryonic stage, raising concerns about their ability to model and treat disease. Here, we report the directed differentiation of hPSCs into medial ganglionic eminence (MGE)-like progenitors and their maturation into forebrain type interneurons. We find that early-stage progenitors progress via a radial glial-like stem cell enriched in the human fetal brain. Both in vitro and posttransplantation into the rodent cortex, the MGE-like cells develop into GABAergic interneuron subtypes with mature physiological properties along a prolonged intrinsic timeline of up to 7 months, mimicking endogenous human neural development. MGE-derived cortical interneuron deficiencies are implicated in a broad range of neurodevelopmental and degenerative disorders, highlighting the importance of these results for modeling human neural development and disease.